Screening for Hemochromatosis: Recommendation Statement

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendation on screening for hemochromatosis and the supporting scientific evidence. The complete information on which this statement is based, including evidence tables and references, is available in the accompanying article in this issue and on the USPSTF Web site (www.preventiveservices.ahrq.gov).

The USPSTF is redesigning its recommendation statement in response to feedback from primary care clinicians. The USPSTF plans to release, later in 2006, a new, updated recommendation statement that is easier to read and incorporates advances in USPSTF methods. The recommendation statement in this paper is an interim version that combines existing language and elements with a new format. Although the definitions of grades remain the same, other elements have been revised.

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* For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.

Summary of the Recommendation

The U.S. Preventive Services Task Force (USPSTF) recommends against routine genetic screening for hereditary hemochromatosis in the asymptomatic general population.

This is a **grade D** recommendation. (See **Appendix Table 1** for a description of the USPSTF classification of recommendations.)

Rationale

Importance: There is fair evidence that disease due to hereditary hemochromatosis is rare in the general population. (See **Appendix Table 2** for a description of the USPSTF classification of levels of evidence.)

Detection: The USPSTF found fair evidence that a low proportion of individuals with a high-risk genotype (C282Y homozygote at the *HFE* locus, a mutation common among white populations presenting with clinical symptoms) manifest the disease.

Benefits of detection and early treatment: There is poor evidence that early therapeutic phlebotomy improves morbidity and mortality in screening-detected versus clinically detected individuals.

Harms of detection and early treatment: Screening could lead to identification of a large number of individuals who possess the high-risk genotype but may never manifest the clinical disease. This may result in unnecessary surveillance, labeling, unnecessary invasive work-up, anxiety, and, potentially, unnecessary treatments.

USPSTF assessment: The USPSTF concludes that the potential harms of genetic screening for hereditary hemochromatosis outweigh the potential benefits.

Clinical Considerations

This recommendation applies to asymptomatic persons. This recommendation does not include individuals with signs or symptoms that would include hereditary hemochromatosis in the differential diagnosis. Furthermore, it does not include individuals with a family history of clinically detected or screening-detected probands for hereditary hemochromatosis.

Clinically important disease due to hereditary hemochromatosis appears to be rare. Even among individuals with mutations on the hemochromatosis (*HFE*) gene, it appears that only a small subset will develop symptoms of hemochromatosis. An even smaller proportion of these individuals will develop advanced stages of clinical disease.

Clinically recognized hereditary hemochromatosis is primarily associated with the *HFE* mutation C282Y. Although this is a relatively common mutation in the U.S. population, great racial and ethnic variations exist. The frequency of homozygosity is 4.4 per 1000 among white persons, with much lower frequencies among Hispanic persons (0.27 per 1000), black persons (0.14 per 1000), and Asian-American persons (<0.001 per 1000). Screening of family members of probands identifies the highest

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prevalence of undetected C282Y homozygotes (23% of all family members tested), particularly among siblings (33% homozygosity).

The natural history of disease due to hereditary hemochromatosis is not well understood but appears to vary considerably among individuals. Clinically recognized hereditary hemochromatosis is about twice as common in men as in women. Iron accumulation and disease expression are modified by environmental factors, including blood loss or donation, alcohol use, diet, and infections such as viral hepatitis. Among C282Y homozygotes newly identified in the general population by genotypic screening, 6% of those undergoing further evaluation had cirrhosis (representing 1.4% of all newly screening-identified C282Y homozygotes). Cirrhosis is a serious, late-stage disease development, and its prevention would be a major goal of screening and treatment.

Individuals with a family member, especially a sibling, who is known to have hereditary hemochromatosis may be more likely to develop symptoms. These individuals should be counseled regarding genotyping, with further diagnostic testing as warranted as part of case-finding.

In addition to genotyping, more common laboratory testing can sometimes identify iron overload. Clinical screening with these laboratory tests, or phenotypic screening, was not included in the evidence synthesis on which this recommendation is based. Genotyping primarily focuses on the identification of the C282Y mutation on *HFE*. While other mutations exist, C282Y homozygosity is most commonly associated with clinical manifestations. Identifying an individual with the genotypic predisposition does not accurately predict the future risk for disease manifestation.

Therapeutic phlebotomy is the primary treatment for hemochromatosis. Treated individuals report inconsistent improvement of their signs and symptoms. It is uncertain whether cirrhosis at diagnosis confers a worse prognosis based on the potential lack of reversibility of liver damage. Recent research reports survival rates in treated individuals with or without cirrhosis that are similar to rates in healthy controls. The degree to which clinically important manifestations can be averted remains uncertain, as does the optimal time for early treatment.

Other Considerations

System issues: Genetic screening for hereditary hemochromatosis is not widespread in the United States.

Value: Systematic screening is potentially costly and may lead to additional diagnostic tests, regular follow-up, and treatment.

Research needs: Longitudinal studies that better define the natural history of the disease and penetrance of the disease among those with specific *HFE* mutations are needed. The effectiveness and optimum timing of therapy need to be determined.

Policy issues: There are important ethical concerns about screening for genetic conditions when the ability to predict the development of disease in those who screen positive is uncertain or very low. Identification of homozygosity could lead to diminished insurability.

Community issues: While clinical disease associated with hereditary hemochromatosis is uncommon, there is significant variation in the prevalence of C282Y homozygotes according to race and ethnicity.

Discussion

Burden of Illness

Iron overload leading to organ damage is the main mechanism associated with morbidity and mortality. Specifically, liver damage associated with cirrhosis and hepatocellular cancer can contribute to decreased life expectancy. Understanding the burden of disease requires both a standardized case definition and longitudinal cohort studies. For this review, the USPSTF defined disease as the presence of clinical signs and symptoms; serum biochemical or genetic abnormalities alone were insufficient. The clinical case definition varies greatly in the literature, from late stages of liver disease to iron overload or elevated serum iron measures. Two retrospective cohort studies followed 33 individuals with C282Y homozygosity for between 17 and 25 years (1, 2). Approximately 25% (8 of 33) were lost to follow-up. Another 25% were women age 50 years or younger at final follow-up, the fifth decade being the time most women begin to present clinically. Of those followed, approximately 75% had elevated serum iron measures. For 10 individuals, iron overload was assessed, with 5 of 6 undergoing a biopsy indicating iron overload. When the 2 studies were combined, approximately one tenth (3 of 33) of individuals had liver disease.

Cross-sectional data obtained from health clinics, blood donor settings, mass screening, and family screening support the incomplete penetrance of C282Y homozygosity, while the actual estimates must be interpreted with caution because of inherent bias in these types of data. Pooled data provided information on 67 771 individuals identified from general screening and 200 family members of probands. A total of 228 (0.3%) individuals were identified as C282Y homozygotes as a result of non–family-based genetic screening. Of those further evaluated, 38% demonstrated iron overload, 25% liver fibrosis, and 6% cirrhosis. A larger proportion of family members of probands had iron overload (49% to 86%) and cirrhosis (8%). Of the 150 individuals identified through family-based screening assessed genetically, 25 were C282Y homozygotes.

Scope

After the discovery of the *HFE* gene and its clinically relevant mutations in 1996, hereditary hemochromatosis was proposed as a potentially ideal model for universal genetic screening of a disease (3). In taking up the issue of screening for hereditary hemochromatosis for the first time, the USPSTF focused its review of evidence on 2 points: first, to determine the actual penetrance of the phenotype among genetically identified individuals; and second, to assess the evidence about the benefits of early treatment to determine whether genetic screening of asymptomatic individuals could lead to a substantial health benefit.

MEDLINE, CINAHL, and Cochrane Library databases from 1996 through February 2005 were reviewed. Supplemental literature was added from examining bibliographies of key reviews and from suggestions by experts in the field (4).

Accuracy of Screening Tests

Because of the targeted nature of this review, the USPSTF did not focus on the accuracy of genetic screening tests. Nor did the USPSTF assess the validity of various combinations of phenotypic and genotypic approaches to screening. Rather, the USPSTF focused on genetic screening for hereditary hemochromatosis, specifically C282Y homozygosity. The USPSTF did not assess the role of increased serum iron measures such as transferrin saturation and serum ferritin in screening. While elevated serum iron measures may provide more "clinically" relevant information about early disease, the predictive value for progression of disease is limited (2).

Intervention and Treatment

Genetic screening for *HFE* mutations can accurately identify individuals at risk for hereditary hemochromatosis, but the predictive value of determining clinically significant disease, especially that associated with liver fibrosis, is low. Beutler and colleagues (5) found that among C282Y homozygotes, 50% demonstrated no elevation in transferrin saturation and 99% were free of clinical symptoms.

Therapeutic phlebotomy is the mainstay of treatment for hereditary hemochromatosis. The goal of therapeutic phlebotomy is to decrease total body iron overload. Phlebotomy is generally thought to have few side effects. However, because the progression from iron overload to clinically significant disease among persons with C282Y/C282Y mutations is uncertain, it is difficult to quantify the potential impact of phlebotomy on all individuals with these mutations. Multiple studies demonstrate that therapeutic phlebotomy does decrease serum iron indices, but data are lacking appropriate control groups. Other studies reporting improved outcomes from phlebotomy also are confounded by unmeasured factors, such as duration of disease, age, and historical factors (for example, hepatitis, alcohol ingestion, and diet). Among individuals with biopsy-proven liver fibrosis, phlebotomy was associated with an improvement of 13% to 50%, with the greatest improvement among individuals with the least degree of liver fibrosis. Individuals served as their own controls, and improvement was based on qualitative histologic measures. When liver fibrosis is present and in its early stages, therapeutic phlebotomy appears to control or slow progression of liver disease (6, 7).

No controlled therapeutic studies were identified among patients with hemochromatosis due to any cause. No studies were found that compared the effectiveness of early as opposed to delayed treatment. Three fair-quality case series of referred patients provided data on 447 individuals (85 with genotypically confirmed hemochromatosis) who underwent phlebotomy (6, 8, 9). These studies demonstrate that the 10-year survival of individuals recently diagnosed with hereditary hemochromatosis or treated prior to the development of cirrhosis does not differ from that in age- and sex-matched population controls; however, no data are available on untreated controls.

Harms of Screening and Treatment

Harms associated with screening are not well studied: Potential harms include the psychological burden of being labeled as having a chronic disease, the potential consequence of this labeling on a person's ability to obtain health or life insurance, and concern associated with genetic testing in the absence of qualified genetic counseling. Phlebotomy, a somewhat invasive procedure, is associated with some harms.

Research Needs

The penetrance of clinical disease among individuals with hereditary hemochromatosis is unknown. It is clear, however, that most of those identified at any point in time with the most common genetic mutation associated with clinical disease (the C282Y mutation) do not manifest clinically significant disease. While further studies on the natural history of untreated individuals who are homozygous for C282Y would provide more precise estimates of penetrance, other questions may be even more relevant to clinical preventive services. As genotyping of individuals becomes more common, understanding the factors that influence phenotypic expression will be critical in assessing an individual's risk for disease. The optimum timing and effectiveness of early therapy need to be established.

Other mutations associated with hereditary hemochromatosis have been identified, but these mutations have low frequencies. There are likely to be some mutations at other gene loci that affect the likelihood of hereditary hemochromatosis that have not been identified.

One study identified treatment harms associated with phlebotomy, but more could be known about 1) the impact of unnecessary procedures (that is, those that have no benefit) and 2) the cost and burden of disease surveillance and monitoring.

Recommendations of Others

Other groups have reviewed the utility of screening for hereditary hemochromatosis. The Centers for Disease Control and Prevention does not recommend universal testing for hereditary hemochromatosis but rather suggests evaluating iron overload in individuals with a family history, and in symptomatic individuals (10). The American College of Physicians found insufficient evidence to recommend for or against the use of transferrin saturation and serum ferritin levels to identify early stages of hereditary hemochromatosis (11). The American Association for the Study of Liver Disease, American College of Gastroenterology, and the American Gastroenterological Association recommend genotyping individuals who have abnormal iron screening tests and first-degree relatives of those identified with C282Y homozygosity (12).

Appendix

Members of the U.S. Preventive Services Task Force are Ned Calonge, MD, MPH, *Chair* (Colorado Department of Public Health and Environment, Denver, Colorado); Diana B. Petitti, MD, MPH, *Vice-Chair* (Kaiser Permanente Southern California, Pasadena, California); Thomas G. DeWitt, MD (Children's Hospital Medical Center, Cincinnati, Ohio); Leon Gordis, MD, MPH, DrPH (Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland); Kimberly D. Gregory, MD, MPH (Cedars-Sinai Medical Center, Los Angeles, California); Russell Harris, MD, MPH (University of North Carolina School of Medicine, Chapel Hill, North Carolina); Kenneth W. Kizer, MD, MPH (National Quality Forum, Washington, DC); Michael L. LeFevre, MD, MSPH (University of Missouri School of Medicine, Columbia, Missouri); Carol Loveland-Cherry, PhD, RN (University of Michigan School of Nursing, Ann Arbor, Michigan); Lucy N. Marion, PhD, RN (School of Nursing, Medical College of Georgia, Augusta, Georgia); Virginia A. Moyer, MD, MPH (University of Texas Health Science Center, Houston, Texas); Judith K. Ockene, PhD (University of Massachusetts Medical School, Worcester, Massachusetts); George F. Sawaya, MD (University of California, San Francisco, California); Albert L. Siu, MD, MSPH (Mount Sinai Medical Center, New York, New York); Steven M. Teutsch, MD, MPH (Merck & Co., Inc., West Point, Pennsylvania); and Barbara P. Yawn, MD, MSc (Olmstead Research Center, Rochester, Minnesota).

This list includes members of the Task Force at the time this recommendation was finalized. For a list of current Task Force members, go to www.ahrq.gov/clinic/uspstfab.htm.

From the U.S. Preventive Services Task Force, Agency for Healthcare Research and Quality, Rockville, Maryland.

Appendix Table 1.* U.S. Preventive Services Task Force Recommendations and Ratings

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*
B	The USPSTF recommends that clinicians provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*
C	The USPSTF makes no recommendation for or against routine provision of [the service]. *The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that [the service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to 1 of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2.* U.S. Preventive Services Task Force Grades for Strength of Overall Evidence

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor).

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